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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/685,986	10/14/2003	Howard I. Katz	17610 (BOT)	7095

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/685,986	**Applicant(s)** KATZ ET AL.
	Examiner Donna Jagoe	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending in this application.

Applicants' arguments filed October 31, 2006 have been fully considered and they are deemed to be persuasive regarding previous rejections of record. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

However, upon reconsideration, the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application. The amendment filed October 31, 2006 has been received and entered. Claims 1, 10, 15, 17 and 19 have been amended.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perel (U) Nissani U.S. Patent No. 6,164,278 A and Borodic U.S. Patent No. 5,298,019 and in further view of Odergren et al. (V).

Perel teaches that parafunctional habits, such as clenching and bruxism are potentially destructive to implant prosthodontic components, causing destruction of bone around implants (page 261). These parafunctional occlusal forces are usually imparted to prostheses nocturnally and can lead to tooth loss. Perel does not teach administration of botulinum toxin.

Nissani teaches that sleep bruxism exerts powerful forces on teeth, gums and joints and causes adverse effects to dental implants and aesthetic restorations (column 1, lines 40-67). Nissani further teaches that some approaches to treat bruxism and clenching involve muscle relaxers, such as magnesium administration (column 4, lines 49-56). Although Nissani teach that muscle relaxers are contemplated, it does not teach administration of botulinum toxin.

Borodic provides motivation to employ a chemodenervating agent such as to botulinum toxin derived preparations (column 2, lines 36-40), injected into the muscles activating the jaw (muscles of mastication) to retard tooth wear caused by involuntary or unconscious clenching of teeth (column 4, lines 18-21). Any type of botulinum toxin may be employed (A through G) (column 3, lines 58-63).

Borodic differs in that it does not teach specifically facilitating an adherence of a dental item to a substrate in the mouth of a patient, however Perel teaches that bruxism and clenching can cause destruction of implants and prosthetic components and Nissani teach that bruxism exerts powerful forces on teeth and gums and is harmful for implants and aesthetic restorations. It would have been made obvious to one of ordinary skill in art at the time it was made to administer botulinum toxin to weaken a muscle of mastication to facilitate the adherence of a dental item, facilitate adherence of a tooth substrate, accelerate adherence of transplanted gum tissue to a substrate in the mouth of a patient and obtain an optimal oral neuromuscular position motivated by the teachings of Borodic that inhibition of jaw clenching protects the teeth when botulinum toxin is administered to the masseter, temporalis and pterygoid muscles (muscles of mastication) of a patient (column 9, lines 30-46). And Perel and Nissani who teach that clenching and bruxism is harmful to prosthetics, gums and aesthetic restorations. In holding an invention obvious in view of a combination of references, there must be some suggestion, motivation or teaching in the prior art that would have led a person of ordinary skill in the art to select the references and combine them in the way that would produce the claimed invention. This motivation may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Here, Perel disclose that bruxism and clenching can cause destruction of implants and prosthetic components. Nissani teach the destructive effect to prosthetics, gums and aesthetic restorations. Borodic discloses inhibition of tooth wear by administration of a chemodenervating agent such as to botulinum toxin derived preparations (column 2, lines 36-40), injected into the muscles activating the jaw (muscles of mastication), such as the masseter, temporalis and pterygoid muscles, to retard tooth wear caused by involuntary or unconscious clenching of teeth (column 4, lines 18-21). In addition, by the time of the claimed invention, botulinum toxin was a well-known and successful chemodenervating agent used in attenuating spasmodic activity of muscle (see Borodic, column 1, line 10 to column 2, line 2). Accordingly, there was clear motivation to employ a botulinum toxin to weaken the muscles of mastication to reduce the bite force that could damage a dental restoration, gum transplant or obtain an optimal oral neuromuscular position when the patients bite position was suboptimal and resulted in damage to the teeth by clenching/grinding. Regarding the dosage of about 1 unit and about 10,000 units, Borodic teaches administration of between a few units to about 1000 units, which is encompassed by the claims dosage amount. Further, as anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. For these and other self-evident reasons, it would have been obvious to use between about 1 unit and about 10,000 units of botulinum toxin.

Regarding the period of time of claims 6 and 14, Odergren et al. teach that the pharmacodynamic properties of botulinum toxin are such that the onset of action is usually evident within two weeks of treatment and the peak effect occurs at four to eight weeks when injected into muscles for cervical dystonia (see page 11, column 2 2nd full paragraph). This time period overlaps and partially encompasses the claimed time period of between one hour and thirty days.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Patent Examiner
Art Unit 1614

May 4, 2007

Ardin H Marschel 5/6/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

Notice of References Cited	Application/Control No. 10/685,986	Applicant(s)/Patent Under Reexamination KATZ ET AL.	
	Examiner Donna Jagoe	Art Unit 1614	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,164,278	12-2000	Nissani, Moti	128/848
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Perel, Morton L., Parafunctional Habits, Nightguards, and Root Form Implants, 1994, Implant Dentistry, Volume 3 No. 4 pages 261-263
	V	Odergren et al., A double blind, randomized, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia, 1998, J. Neurol Neurosurg Psychiatry Vol 64 pages 6-12.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

U.S. Patent and Trademark Office
PTO-892 (Rev. 01-2001) Notice of References Cited Part of Paper No. 20070502

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J Neurol Neurosurg Psychiatry 1998;64:6–12

A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport® and Botox® in the treatment of cervical dystonia

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Abstract

Objective—**This study was designed to establish whether a ratio of three units of Dysport® is equivalent to one unit of Botox® for the treatment of cervical dystonia.**

Methods—**Patients with predominantly rotational cervical dystonia, and a minimum of four previous Botox treatments, were randomised to receive either the clinically indicated dose of Botox or three times that dose in Dysport units. Study botulinum toxin was administered in a double blind fashion, to one or more clinically indicated muscles, at one or more sites per muscle. Patients returned for assessment two, four, eight, and 12 weeks after treatment.**

Results—**A total of 73 patients (Dysport, 38; Botox, 35) were entered. The Dysport group received a mean (SD) dose of 477 (131) (range 240–720) Dysport units, and the Botox group received a mean (SD) dose of 152 (45) (range 70–240) Botox units. The mean (SEM) post-treatment Tsui scores for the Dysport group (4.8 (0.3)) and the Botox group (5.0 (0.3)) were not statistically different (p=0.66). The study had 91% power to detect a clinically significant difference of two points. Both groups showed substantial improvement in Tsui score by week 2 (mean (SD)); Dysport, 46 (28)%; Botox, 37 (28)%), with a peak effect at week 4 (mean (SD)); Dysport, 49 (29)%; Botox, 44 (28)%). A similar response profile was seen for other assessments of efficacy. The duration of effect, assessed by time to retreatment, was also similar (mean (SD)); Dysport, 83.9 (13.6) days; Botox, 80.7 (14.4) days; p=0.85). During the study 22 of 38 (58%) Dysport patients reported 39 adverse events, and 24 of 35 (69%) Botox patients reported 56 adverse events (p=0.35). A global assessment of efficacy and safety considered that 29 of 38 (76%) Dysport patients and 23 of 35 (66%) Botox patients were treatment successes (p=0.32).**

Conclusion—**Patients with predominantly rotational cervical dystonia treated with the clinically indicated dose of Botox or three times that dose in Dysport units show similar improvements and do not have significantly different safety profiles.**

(*J Neurol Neurosurg Psychiatry* 1998;64:6–12)

Keywords: botulinum toxin; cervical dystonia; bioequivalence

Botulinum toxin type A is a potent neurotoxin isolated from *Clostridium botulinum*. Despite its highly toxic nature, botulinum toxin has therapeutic applications, and it has become the treatment of choice for many dystonic conditions, including cervical dystonia.[1]

Cervical dystonia is characterised by sustained involuntary contractions of the cervical muscles leading to painful and disabling postures. Rotation of the chin and tilt, flexion, or extension of the head are thus present either in isolation or in various combinations. A prevalence of 89/million population has been reported.[2]

Botulinum toxin therapy induces a temporary, partial chemodenervation of the injected muscles.[3] Injection into cervical muscles causes relaxation in muscle tone and fibre atrophy and reduces motor unit potential size,[4] thereby decreasing the force of muscle contraction. This produces relief from pain, increased range of free movement, improved resting posture, and less overall disfigurement, leading to improved quality of life for most patients.

Dysport® and Botox® are the two preparations of botulinum type A toxin commercially available at present. It is clear from the literature and from clinical experience that the units used to quantify the toxin activity of the two products are not equivalent. This apparent difference in the potency of the two products causes difficulties when comparing the results of studies using the different preparations, and when changing from one preparation to the other. It is likely that any difference between the two products is the result of the different assay methods used to quantify the activity of the products,[5] and a bioequivalent ratio of one Botox unit to three Dysport units has been suggested.[6 7]

This study was designed to compare a clinically established dose of Botox with three times that dose in Dysport units in the treatment of patients with predominantly rotational cervical dystonia.

Methods

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the Declaration of Helsinki and its amendments, as well as the guidelines for good clinical practice. It was approved by the appropriate national regulatory organisations and local research ethics committees. The study was explained fully to eligible patients, and written informed consent was obtained before any study specific assessments were performed.

STUDY POPULATION

Patients were required to have predominantly rotational cervical dystonia, with involuntary contractions of a constant duration, as defined by Tsui *et al.*[8] In addition, a minimum of four previous Botox treatments were required, with the latest being within 10–16 weeks of study treatment.

Patients with other forms of cervical dystonia were thus excluded, as were patients who required more than 250 units of Botox, or a dose of Botox 100 units more than a previous dose shown to be effective. Other exclusion criteria were hypersensitivity to botulinum toxin, swallowing abnormalities (moderate difficulty in swallowing liquids or solids), pregnancy or breastfeeding, myasthenia gravis or other disease of the neuromuscular junction, and unwillingness or inability to comply with the protocol. Any patient who had taken an investigational new drug (a new chemical entity not registered for use) in the preceding three months, or was due to receive such a drug during the study period, was also excluded.

TSUI SCORE

The total Tsui score[8] (0–25) was calculated using the equation $(A \times B) + C + D$, where each component of the equation was made up as follows:

A=Amplitude of sustained movements: a combined score made up from assessment of the amplitude of rotation, laterocollis, anterocollis, and retrocollis, which were scored from 0–3 (0=absent, 1<15°, 2=15–30°, 3>30°).

B=Duration of sustained movements, where 0=none, 1=intermittent, and 2=constant.

C=Shoulder elevation, where 0=absent, 1=mild and intermittent, 2=mild and constant, or severe and intermittent, and 3=severe and constant.

D=Tremor, which was calculated by multiplying the severity of tremor (0=none, 1=mild, 2=severe) by the duration (0=none, 1=occasional, 2=continuous).

The inclusion criteria required patients to have a predominantly rotational form of cervical dystonia, as defined by a rotation score of at least 1, a laterocollis score no greater than the rotation score, a retrocollis score of no more than 1, and an anterocollis score of 0.

ASSESSMENTS AT ENTRY (WEEK 0)

Demographic data (sex, date of birth, weight, height, race) and vital signs (heart rate, systolic/diastolic blood pressure, temperature) were assessed and recorded. Other data collected included the date that cervical dystonia was first diagnosed, whether the patient had any other type of dystonia, or if any relative also had cervical dystonia. Also recorded were the date of the patient's first Botox treatment, their total number of treatments, the cumulative dose of Botox injected, the maximum single dose injected, and the date, dose, and injection sites of the most recent Botox injection.

The signs and symptoms of cervical dystonia were assessed, and the total Tsui score was calculated. Pain associated with cervical dystonia was assessed by the patient as none, mild, moderate, or severe.

Details of all medical events experienced by the patient, and all concomitant medication received by the patient during the seven days prior to entry were recorded.

ASSESSMENTS AT WEEKS 2, 4, 8, AND 12

Tsui score and pain associated with cervical dystonia were assessed and recorded as described previously. In addition, both the patient and the investigator assessed cervical dystonia symptoms in relation to the symptoms at entry before receiving study toxin (symptom free, improvement >50%, improvement <50%, no improvement, or worse).

Adverse events either seen by the investigator or reported by the patient were assessed and recorded. As well as the diagnosis, each adverse event was assessed for intensity (mild, moderate, severe), seriousness (not serious, serious), action taken (none, treatment, other), duration, and relation to the study drug (probable, possible, unlikely, unrelated). Vital signs and changes in concomitant medication were also assessed and recorded.

ASSESSMENTS ON COMPLETION OF THE STUDY

Study completion occurred at the week 12 assessment, or earlier if patients required retreatment. The need for retreatment was based on a global clinical evaluation of each patient, and the protocol allowed patients to be re-treated as early as week 8. Patients who were not re-treated at week 12 were followed up until week 16 to collect retreatment details. The date of re-treatment, or the reason for not re-treating, was recorded for each patient.

On completion of the study the investigator made a global assessment of the efficacy and safety of the study toxin. Efficacy was assessed on a six point scale (excellent, good, moderate, slight improvement, no change, or worse). Safety was assessed in terms of adverse events on a five point scale (none, mild, moderate, severe, or extreme). Patients were considered a treatment success if the efficacy assessment was excellent, good, or moderate, and the safety assessment was none, mild, or moderate.

STUDY TOXINS

Dysport (Speywood Pharmaceuticals Ltd, Maidenhead, UK) was supplied in clear glass vials as a freeze dried white pellet containing *Clostridium botulinum* type A toxin haemagglutinin complex together with 125 μg human albumin and 2.5 mg lactose. Each vial contained 500 Dysport units. It was recommended that vial contents should be reconstituted in sodium chloride injection BP (0.9%), and used within one hour.

Botox (Allergan Inc, Irvine, California, USA) was supplied from commercial stock as a crystalline complex containing *Clostridium botulinum* type A toxin with an associated haemagglutinin protein, 500 µg human albumin, and 0.9 mg sodium chloride. Each glass vial contained 100 Botox units. It was recommended that the vial contents should be reconstituted according to the manufacturer's instructions.

RANDOMISATION, BLINDING, AND ADMINISTRATION OF STUDY TOXIN

The doses used in this study were not fixed, but based on the clinical need of each patient. At entry, the investigator assessed the clinical symptoms of the patient and reviewed previous responses to treatment, to determine the next clinically indicated dose and the most appropriate injection sites. Eligible patients were randomised to receive either the clinically indicated Botox dose or three times that dose in Dysport units. Before the start of the study a randomisation list was generated in blocks of four patients and each centre was allocated sufficient patient numbers, with individual patient randomisation envelopes.

Blinding of the study medication was the responsibility of the study pharmacist. This role was performed by the hospital pharmacy at the five Swedish centres, and by a designated study nurse at the two Finnish centres. The study pharmacist was not involved with patient management or assessment. Once the investigator informed the study pharmacist of the proposed dose for the patient, the study pharmacist opened the next randomisation envelope, which allocated either Dysport or Botox treatment, and prepared a syringe with the appropriate dose of study toxin. Injection volume was determined by the proposed Botox dose (1ml/100 units), regardless of actual study toxin, thereby maintaining the study blind.

Treatment was administered by intramuscular injection to one or more muscles as clinically indicated, and each muscle could be injected at more than one site. No further botulinum toxin treatment was given until the end of the study. Only the clinically indicated Botox dose and the muscles injected were recorded. The investigator remained blinded throughout the study, and was only made aware of treatment allocation at the end of the study when all data were ready for analysis.

STATISTICAL ANALYSIS

Two primary efficacy variables were identified by the protocol: the mean post-treatment Tsui score up to week 12 or until retreatment if this was before week 12, and the time between administration of study toxin and re-treatment.

The sample size calculation was based on the mean post-treatment Tsui scores. It was planned to recruit 90 patients (45 patients/group) to ensure that the study would have 90% power to detect a clinically significant between group difference ($\alpha=0.05$, two tailed test) in the mean post-treatment Tsui score of two or more points, assuming an SD of three points. The study was brought to a close once all available eligible patients had been recruited from the participating centres. Despite not recruiting 90 patients, the primary efficacy index was less variable than predicted, such that with 73 patients the study had 91% power.

Plans for the statistical analysis of the study were summarised in the protocol and presented in detail in a prospective analysis plan. No changes were made to this plan after the unblinding of the study.

All randomised patients also received study medication, and completed the study. All patients, therefore, were included in the efficacy and safety analyses. Due to a between group difference in Tsui score at entry, and between group differences in the mean post-treatment Tsui score at some centres, the overall analysis of the mean post-treatment Tsui score was performed using analysis of covariance (ANCOVA). The time to re-treatment was compared between groups using a Cox proportional hazards survival analysis, and the investigator's global assessment (success/failure) was compared between groups using the χ^2 test. Treatment groups were also compared statistically for the overall incidence of adverse events, as well as the incidence of each of the main adverse events. Other data have been summarised only.

Results

PATIENT DISPOSITION

A total of 73 patients (Dysport, 38; Botox, 35) entered the study at seven centres (five Swedish, two Finnish), who recruited totals of 21 (29%), 14 (19%), 12 (16%), nine (12%), eight (11%), five (7%), and four (5%) patients. All patients were treated and there were no withdrawals. Two Dysport patients and five Botox patients completed the study at week 8, and therefore did not have an assessment at week 12.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 1 shows a summary of patient demographics, cervical dystonia history, previous toxin treatment, and cervical dystonia symptoms at entry. Overall, the two treatment groups were well matched. The between group difference in Tsui score of 1.1 points suggests that the status of the Botox group may have been slightly worse at entry. Also, a higher proportion of patients were female in the Dysport group, the time since diagnosis of cervical dystonia was slightly shorter in the Dysport group, and fewer Dysport patients had other dystonias or a family history of cervical dystonia. At entry 24 of 38 (63%) patients in the Dysport group were receiving a total of 62 concomitant medications, and 22 of 35 (63%) patients in the Botox group were receiving a total of 44 concomitant medications. The most often used concomitant medications were analgesic, antidepressant, antiepileptic, and neuroleptic drugs, and sedatives. Anticholinergic drugs were used by only three patients in each group.

STUDY TOXIN TREATMENT

Patients in the Dysport group received a mean (SD) dose of 477 (131) (range 240–720) Dysport units, and patients in the Botox group

Table 1 Demographic and baseline data

	Dysport	*Botox*
No of patients	38	35
Age (y)	51.3 (11.0) (31-78)	51.4 (10.4) (26-70)
Female (n (%))	29 (76)	19 (54)
Height (cm)	169 (8) (155-187)	170 (8) (154-187)
Weight (kg)	71 (12) (49-105)	69 (10) (54-98)
Time since cervical dystonia diagnosed (months)	103 (104) (30-571)	132 (97) (15-408)
Patients with other dystonia (n (%))	2 (5)	4 (11)
Family history of cervical dystonia (n (%))	4 (11)	9 (26)
Time since first Botox treatment (months)	42 (14) (7-73)	43 (18) (10-75)
Total number of Botox treatments	14.1 (5.7) (4-31)	15.9 (7.6) (5-30)
Total dose of Botox prior to entry (units)	1751 (884) (345-4980)	2007 (1110) (370-4115)
Maximum single dose of Botox (units)	168 (42) (90-250)	166 (44) (90-275)
Most recent Botox dose (units)	152 (43) (60-240)	148 (43) (50-240)
Time since most recent Botox treatment (days)	96 (19) (62-149)	91 (22) (28-135)
Tsui score at entry	7.4 (2.5) (3-14)	8.5 (2.4) (4-14)
Proportion of pain free patients at entry (n (%))	12 (32%)	11 (31%)

Values are presented as mean (SD) (range) or n (%).

received a mean (SD) dose of 152 (45) (range 70–240) Botox units. Similar proportions of patients in each group received injections in the sternocleidomastoid (Dysport, 35 of 38, 92%; Botox, 34 of 35, 97%), splenius capitis (Dysport, 36 of 38, 95%; Botox, 30 of 35, 86%), trapezius (Dysport, 25 of 38, 66%; Botox, 23 of 35, 66%), and levator scapulae (Dysport, 17 of 38, 45%; Botox, 12 of 35, 34%). Injection of the sternocleidomastoid, splenius capitis, and trapezius was the most common combination for both groups (Dysport, 14 of 38, 37%; Botox, 11 of 35, 31%).

PRIMARY EFFICACY VARIABLES

The post-treatment Tsui scores showed a between group difference of one point (mean (SD): Dysport, 4.8 (2.4); Botox, 5.8 (2.6)). When adjusted for baseline and centre effects (mean (SEM): Dysport, 4.8 (0.3); Botox, 5.0 (0.3)); the difference of 0.2 points was not significant (p=0.66). The study had 91% power to detect a between group difference of two points.

All Dysport patients and 33 of 35 (94%) Botox patients were re-treated with botulinum toxin at the end of the study. One Botox patient was not re-treated due to suspected pancreatic carcinoma, which was subsequently rediagnosed as pancreatic inflammation. The other Botox patient was not re-treated within the time frame of this study because benefit was still apparent at week 16. The mean time to re-treatment was three days shorter in the Dysport group (mean (SD), range; Dysport, 84 (14), 56–122; Botox, 81 (14), 49–111)), although this was not significant (p=0.85). Including the seven patients (Dysport, two; Botox five) re-treated at week 8, a total of 10 of 38 (26%) Dysport patients and 11 of 35 (32%) Botox patients required re-treatment earlier than the scheduled week 12 visit. Also, five of 38 (13%) Dysport patients and three of 35 (9%) Botox patients were re-treated after week 12.

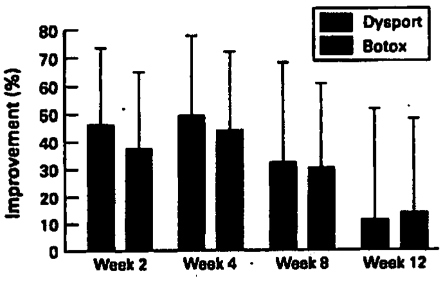

Figure 1 Mean (SD) percentage improvement in Tsui score compared with baseline at weeks 2, 4, 8, and 12.

SECONDARY EFFICACY VARIABLES

Figure 1 presents the percentage improvements in Tsui score. Despite the difference of 1.1 points at entry, the magnitude and profile of the response to study toxin were very similar for both groups. Tsui scores had greatly decreased at week 2 (mean (SD): Dysport, 4.0 (2.2); Botox, 5.4 (3.0)), with the peak response being found at week 4 (mean (SD): Dysport, 3.8 (2.3): Botox, 4.7 (2.7)). Tsui scores increased at week 8 (mean (SD): Dysport, 5.1 (3.1); Botox, 5.9 (3.0)), and increased further by week 12 (mean (SD): Dysport, 6.2 (2.9); Botox, 7.2 (3.4), but did not reach baseline levels for either group.

Figure 2 shows details of the pain associated with cervical dystonia at each visit. Both groups had a similar proportion of pain free patients at entry, and similar proportions reported mild, moderate, or severe pain. The proportion of pain free patients in each group was considerably higher than baseline at week 2, and had decreased almost to baseline levels by week 12. Figure 3 shows investigator assessments of change in cervical dystonia symptoms since

Table 2 Adverse events

Adverse event	*Dysport (n=38)*	*Botox (n=35)*
Dysphagia	6 (16)	4 (11)
Pharyngitis	4 (11)	6 (11)
Headache	3 (8)	6 (17)
Fatigue	3 (8)	4 (11)
Upper respiratory tract infection	4 (8)	3 (9)
Neck pain	3 (8)	1 (3)
Dry mouth	0 (0)	3 (9)
Muscle weakness	3 (8)	0 (0)
Diarrhoea	1 (3)	2 (6)
Migraine	3 (3)	0 (0)
Coughing	0 (0)	2 (6)
Dysphonia	0 (0)	2 (6)
Epistaxis	2 (5)	0 (0)
Urinary tract infection	0 (0)	2 (6)
Others*	7 (16)	21 (40)
Total	39 (58)	56 (69)

* Adverse events reported just once by one or both groups.
Values are presented as the number of adverse events reported and the percentage of patients reporting them (the same adverse event could be reported more than once by the same patient).

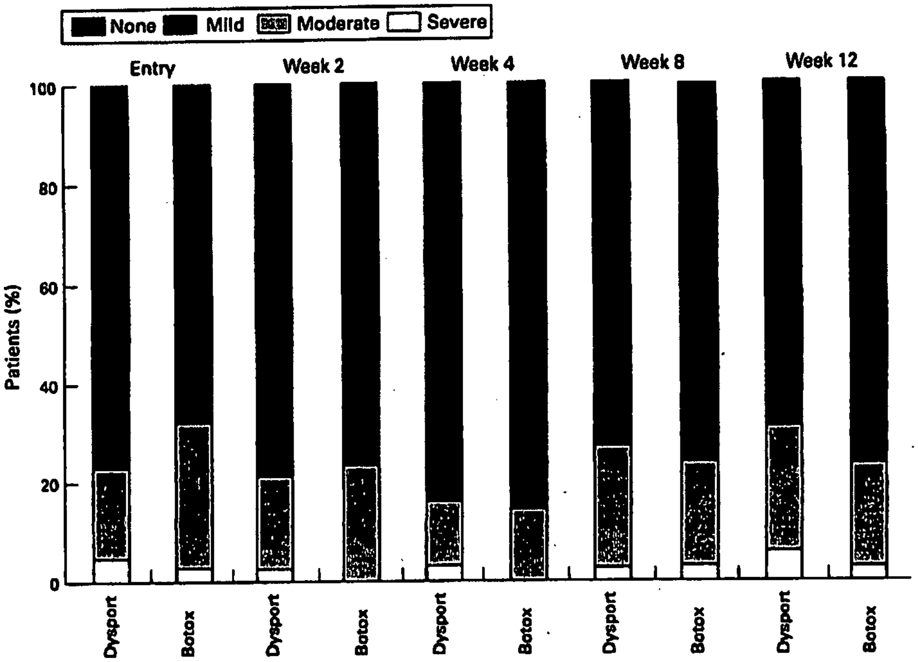

Figure 2 Patient assessment of the severity of pain associated with cervical dystonia.

entry. Most patients in both groups had improved by week 2 (Dysport, 32 of 38, 85%: Botox, 29 of 35, 83%). Although a similar proportion of patients in both groups still had improved cervical dystonia symptoms at week 4, there were more patients with a greater than 50% improvement in the Dysport group. No patient was considered symptom free at any point during the study. At each visit, investigator assessment of the proportion of patients with improved symptoms, was marginally higher than the proportion suggested by patient self assessment. The response profiles, however, were very similar with the peak effect occurring by week 4, when investigators reported that 63 of 73 (86%) patients had improved, compared with 55 of 73 (76%) patients after patient self assessment.

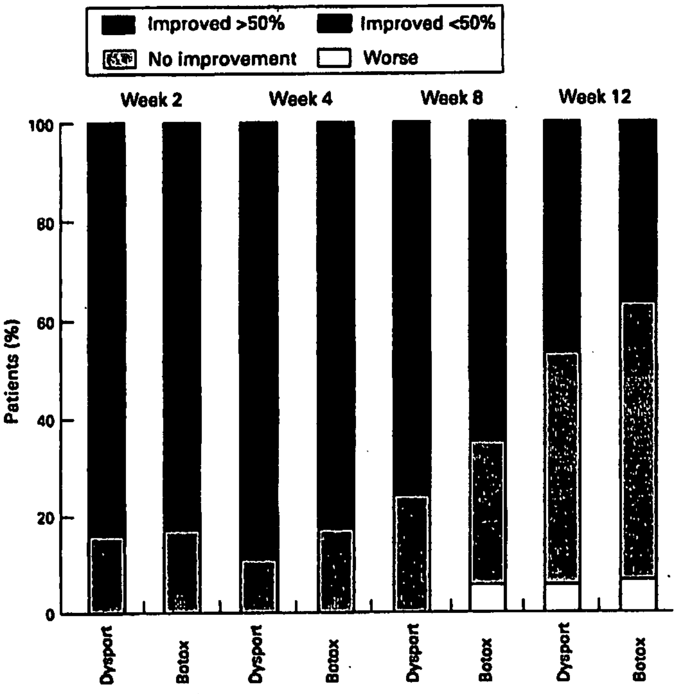

Figure 3 Investigator assessment of change in cervical dystonia symptoms since entry.

SAFETY ASSESSMENT

Table 2 summarises adverse events. Overall, 39 adverse events were reported by 22 of 38 (58%) patients in the Dysport group, and 56 adverse events were reported by 24 of 35 (69%) patients in the Botox group ($p=0.35$). Treatment groups were not statistically different with regard to any individual adverse event ($p>0.05$). The proportion of adverse events reported as mild (Dysport, 23 of 39, 59%; Botox, 37 of 56, 66%), moderate (Dysport, 14 of 39, 36%; Botox, 18 of 56, 32%), and severe (Dysport, two of 39, 5%; Botox, one of 56, 2%) were similar for both groups. One serious adverse event was reported for a Botox patient after diagnosis of pancreatic cancer, although this was later rediagnosed as pancreatic inflammation. Seven adverse events reported by five Dysport patients, and 10 adverse events reported by eight Botox patients required concomitant medication.

Investigators considered that 14 adverse events reported by 12 of 38 (32%) Dysport patients, and 18 adverse events reported by nine of 35 (26%) Botox patients, were possibly or probably related to the study toxin. Dysphagia (Dysport, six; Botox, four) was the most common toxin related adverse event in both groups. The incidence of adverse events during the first four weeks after study toxin administration was also assessed. Both groups were well matched with 17 of 38 patients (45%) in the Dysport group reporting 27 adverse events, and 18 of 35 patients (51%) in the Botox group reporting 30 adverse events. Dysphagia (Dysport, five; Botox, four) and pharyngitis (Dysport, four; Botox, five) were the most commonly reported adverse events in the first four weeks.

GLOBAL EFFICACY AND SAFETY ASSESSMENT

Although there were a greater number of treatment successes in the Dysport group (29 of 38, 76.3%) compared to the Botox group (23 of 35, 65.7%), the difference was not significant ($p=0.32$).

Discussion

The effectiveness and safety of Dysport and Botox have been well established in patients with cervical dystonia, and although the potencies of the two preparations are both assessed using a mouse LD_{50} test, it is clear that one unit of Dysport is not the same as one unit of Botox. Attempts to explain this discrepancy have focused on bioassay technique differences[5]; however, this does not help physicians determine the clinically equivalent doses of the two preparations.

The results of this study provide substantial evidence that three units of Dysport are clinically equivalent to one unit of Botox. This 3:1 bioequivalence ratio is supported by clinical studies in blepharospasm and hemifacial spasm,[6] and also in spasmodic dysphonia.[7] Another open study could not detect treatment differences with a 4:1 ratio in patients with blepharospasm and hemifacial spasm.[9] There has even been a report[10] suggesting the bioequivalence ratio could be as high as 6:1, although this was based on few patients overall, and particularly small numbers of patients receiving Dysport. This is the first randomised double blind study to consider the question of bioequivalence. It is also the first to control for the injection volume, and to apply statistical methodology to the calculation of sample size and the analysis of results.

Non-responsiveness to botulinum toxin is a minor problem, but it was none the less a potential source of error for this study. Consequently, primary non-responders were excluded from the study by the requirement for all patients to have demonstrated a response to botulinum toxin treatment, and the chance of including secondary non-responders was greatly reduced by excluding patients requiring a dose of Botox 100 units more than a previous dose shown to be effective. The dose of botulinum toxin is often adjusted during the first few treatments to define the optimum dose. The requirement for a minimum of four previous toxin treatments, therefore, increased the probability that patients received the optimum dose based on previous clinical experience.

The selection of patients with primarily rotational cervical dystonia reflected the need to ensure a homogenous patient population. Patients with other forms of cervical dystonia, as well as being less common, also require injection of different muscle groups, thereby making comparisons more difficult, especially with regard to side effects. Furthermore, as rotation is a major component of the Tsui score, it could be expected that treatment effects and between group differences would be more easily detected in patients with a primarily rotational cervical dystonia. However, there is no reason to think that the results of this study are not equally applicable to other forms of cervical dystonia.

It is clear from the results of a recent Dysport dose ranging study that patients with rotational cervical dystonia show dose responsiveness between 250 and 1000 Dysport units,[11] so although the dose ranges in this study were 240–720 Dysport units and 70–240 Botox units, it is likely that the 3:1 bioequivalence ratio will also apply at dose levels above and below those used in this study.

The duration of the study and the timing of the assessments were determined by the well established pharmacodynamic properties of botulinum toxin in this patient population. The onset of action is usually evident within two weeks of treatment, the peak effect occurs at four to eight weeks, and most patients require retreatment after 10–16 weeks. For both groups, and for all assessments of efficacy, the effect of study toxin was evident at week 2, with a peak effect occurring at week 4. The duration of benefit from study toxin was assessed by recording the time to re-treatment, which ideally is determined purely on the basis of clinical need. However, in reality the time to re-treatment is also influenced by the practicalities of attending out patient clinics, and in this study most patients were re-treated at their scheduled week 12 visit, which may have reduced the possibility of detecting a difference between groups. However, as both groups had similar proportions of patients who were treated earlier or later than week 12 there is no evidence to suggest that either toxin has a longer duration of benefit.

Several rating scales are available for assessing symptoms and signs of cervical dystonia, but there is no generally accepted gold standard.[12] The widely used scale described by Tsui *et al*[8] shows good interrater reliability, and improvements produced by botulinum toxin have been shown to correlate with subjective efficacy assessments.[13] It was therefore considered to be the most appropriate scale for a multicentre study. It should be noted that although interrater reliability was not assessed, all investigators were familiar with the scale, and the study was designed to assess the change in Tsui score after treatment rather than absolute values. The Toronto western spasmodic torticollis rating scale (TWSTRS)[12] is a more recent development with potentially higher interrater reliability. A comparison of the Tsui and TWSTRS scales, however, has shown that both adequately assess the improvement of cervical dystonia after botulinum toxin treatment.[14] Indeed, the mean Tsui scores at entry in the present study were very similar to that reported by Tarsy,[14] suggesting that the choice of patient population and primary efficacy variable were adequate to be able to determine the treatment response to botulinum toxin. It should be noted that the baseline Tsui scores for patients in this study could well have been higher if there had been no prior exposure to botulinum toxin. The sample size was based on the mean post-treatment Tsui score, which was considered to be an appropriate assessment that reflected the time to onset of effect, the peak effect, and also the duration of the effect.

This study was designed to have 90% power to be able to detect a clinically significant between group difference in mean post-treatment Tsui score of two points, and despite having fewer patients than planned the study actually had 91% power. Once adjusted for baseline differences and centre effects the between group difference of 0.2 points was neither statistically nor clinically significant. This study has not shown that the potency of three Dysport units is identical to the potency of one Botox unit. Rather it has provided an indication of the clinical equivalence of the two formulations of botulinum toxin. As the effect of the two toxins was so similar in this study it is unnecessary to determine the ratio that gives identical potency. It would also be impractical as the present study would have required a total of 6812 patients (3406/group) for the between group difference to be statistically significant at the 95% level. Whether a similarly designed study with a different dose ratio would detect significant differences remains to be determined.

After injection of botulinum toxin some patients experience pain or irritation at the injection site, and it is not unusual to find the unintentional weakening of muscles in close proximity to the target muscles. The typical profile of botulinum toxin related adverse events has been shown by large postmarketing surveillance studies as well as smaller clinical trials,[11] and includes dysphagia, neck weakness, voice changes, and dry mouth or throat. There have also been reports of more distant adverse events, possibly related to the systemic spread of the toxin, including flu-like symptoms,[15] autonomic effects,[16] and subclinical disturbance of neuromuscular transmission.[17] The adverse event profiles found in both groups were consistent with the expected profiles of predominantly local adverse events. Although more adverse events were found in the Botox group over the whole study period, it is noteworthy that the adverse event profiles were well matched during the first four weeks after toxin administration, when adverse events related to toxin would be most likely to occur.

In conclusion, the evidence from this study indicates that patients with predominantly rotational cervical dystonia treated with the clinically indicated dose of Botox or three times that dose in Dysport units show similar improvements and do not have significantly different safety profiles.

1 American Academy of Neurology Therapeutics and Technology Assessment Subcommittee. Assessment: the clinical usefulness of botulinum toxin-A in treating neurologic disorders. *Neurology* 1990;40:1332–6.

2 Nutt JG, Muenter MD, Aronson A, Kurland LT, Melton LJ. Epidemiology of focal dystonia in Rochester, Minnesota. *Mov Disord* 1988;3:188–94.

3 Coffield JA, Considine RV, Simpson LL. The site and mechanism of action of botulinum neurotoxin. In: Jankovic J, Hallett M, eds. *Therapy with botulinum toxin*. New York: Marcel Dekker, 1994:3–15.

4 Odergren T, Tollbäck A, Borg J. Electromyographic single motor unit potentials after repeated botulinum toxin treatments in cervical dystonia. *Electroencephalogr Clin Neurophysiol* 1994;93:325–9.

5 Hambleton P, Pickett AM. Potency equivalence of botulinum toxin preparations. *J R Soc Med* 1994;87:719.

6 Marion MH, Sheehy M, Sangla S, Soulayrol S. Dose standardisation of botulinum toxin. *J Neurology Neurosurg Psychiatry* 1995;59:102–3.

7 Whurr R, Brookes G, Barnes C. Comparison of dosage effects between the American and the British botulinum toxin A product—in the treatment of spasmodic dysphonia. *Mov Disord* 1995;10:56.

8 Tsui JKC, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;ii:245–7.

9 Sampaio C, Ferreira JJ, Simoes F, Rosas MJ, Magalhaes M, Bastos-Lima A, Castro-Caldas A. Dysbot: a single blind, randomised clinical trial to compare two different formulations of botulinum toxin type A. *Mov Disord* 1995;10:57.

10 Durif F. Clinical bioequivalence of the current commercial preparations of botulinum toxin. *European Journal of Neurology* 1995;2:17–8.

11 Poewe W, Deuschl G, Nebe A, *et al*. What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging study using Dysport®. *J Neurol Neurosurg Psychiatry* 1997;64:13–17.

12 Consky ES, Lang AE. Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallett M, eds. *Therapy with botulinum toxin*. New York: Marcel Dekker, 1994:211–37.

13 Odergren T, Tollbäck A, Borg J. Efficacy of botulinum toxin for cervical dystonia. A comparison of methods for evaluation. *Scand J Rehabil Med* 1994;26:191–5.

14 Tarsy D. Comparison of clinical rating scales in the treatment of cervical dystonia with botulinum toxin. *Mov Disord* 1997;12:100–2.

15 Girlanda P, Vita G, Nicolosi C, Milone S, Messina C. Botulinum toxin therapy: distant effects on neuromuscular transmission and autonomic nervous system. *J Neurol Neurosurg Psychiatry* 1992;55:844–5.

16 Claus D, Druschky A, Erbguth F. Botulinum toxin: influence on respiratory heart rate variation. *Mov Disord* 1995;10:574–9.

17 Olney RK, Aminoff MJ, Gelb DJ, Lowenstein DH. Neuromuscular effects distant from the site of botulinum neurotoxin injection. *Neurology* 1988;38:1780–3.

PARAFUNCTIONAL HABITS, NIGHTGUARDS, AND ROOT FORM IMPLANTS

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Occlusal schemes and designs of fixed and removable implant prostheses must satisfy requirements for the innocuous vertical loading of root form implants. Parafunctional habits (clenching, bruxing, or engaging) can transmit forces to the supporting bone that may result in destructive lateral stresses and overloading. Most nocturnal parafunctional habits can be ameliorated by acrylic resin nightguards. (Implant Dent 1994;3:261–263)

Overloading and lateral stresses, with or without a periodontal initiating component, can cause a significant amount of bone loss around root form implants.[1, 2] Jacobs and van Steenberghe[3] discussed the reduced tactile function of oral implants compared to natural teeth. Their study reported that the passive threshold level for oral implants was about 50 times higher than that of teeth, which implies that small loads encountered during oral function might not be quickly perceived by patients with implant-supported prostheses.

Bidez and Misch[4, 5] have shown that internal stresses that develop in an implant and its surrounding biological tissues under an imposed load may have a significant influence on longevity. The investigators are especially concerned with shear forces that typically act parallel to the surface or plane of interest and also are destructive with respect to maintenance of a contiguous bone-to-implant interface.

Meffert[6] has stated that "Generally, the greater the magnitude of stress applied to a dental implant system, the greater the difference in strain between the implant material and bone. In such cases, the less likely the implant will stay attached to the bone and the greater the probability of fibrous tissue ingrowth into the interfacial region to accommodate the range of difference."

PARAFUNCTION

Definitions

Parafunction has been defined as disordered or perverse function. Clenching is defined as the exertion of force in a static tooth-to-tooth relationship, whereas bruxism is the parafunctional grinding of teeth.[7] Broader definitions are useful to describe the nature of parafunctional habits.[8] Clenching is the sustained clamping of the maxillary and mandibular dentition. Bruxism is the nonmasticatory grinding in lateral or lateral-protrusive movements of opposing occlusal tables. Engaging is the interdigitated clamping of opposing teeth and the rocking of the supporting teeth or implants without the actual lateral movements found in bruxism.

Clinical Significance

Parafunctional habits are potentially destructive to implant prosthodontic components (such as screws) by causing metal fatigue. Fortunately, damaged components can usually be replaced. Monteith[9] has stated that implant-supported prostheses must be able to withstand the load capabilities of individual patients to overload them. Of more concern is the destruction of bone around otherwise well-integrated implants. The stresses imparted to the bone may cause an osseointegrated implant to loosen and eventually fail. With stress-induced patterns of bone loss around an implant, treatments that are commonly prescribed for ailing and failing implants are of no value.

Although occlusal schemes and tables may be designed to protect the integration of root form implants,[10] parafunctional habits may impose an overbearing load resulting in significant bone loss.[11] Although bone loss patterns around root form implants have yet to be defined and codified, the concept of retrograde peri-implantitis gives credence to the nature of bone loss that did not originate from pure periodontal pathoses.

Yukna[12] has noted that bruxism and/or clenching is an important factor in implant maintenance because of the possibilities of occlusal overload. He believes that most patients have parafunctional habits and clinicians do not regularly identify this activity in their patients. In the case of parafunctional habits, Yukna recommends placing additional implants, considering opposing occlusion, using a removable prosthesis or a softer type of restorative material, and using a nightguard.

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MICROMOTION AND OVERLOADING

Bone loss patterns from excessive stresses around root form implants do not appear to have a predilection for commercially pure titanium, titanium alloy, or hydroxyapatite-coated titanium. Regardless of root form implant material(s), forces of occlusion and the resultant stresses imparted through the implant, abutment, and superimposed prosthesis to the osseous housing can range biomechanically from micromotion to overloading.

Although we do not know what too much micromotion is, Brunski[13] believes that micromotion can be deleterious at the bone-implant interface, especially if it occurs soon after implantation. Meffert[6] reported that retrograde peri-implantitis may occur due to microfractures in the bone from overloading, too early loading, or lateral forces. Due to the lack of a peri-implant ligament, lateral forces on implants appear to be particularly destructive if unmitigated.

Parafunctional occlusal forces are usually imparted to prostheses nocturnally and can lead to tooth loss. With the partially edentulous arch, wear facets and tooth mobility may be indicative of parafunction. There is rarely any indication of whether the patient is a clencher or a bruxer regardless of the amount of bone loss in the completely edentulous arch. Parafunctional habits have often not been considered to be a contraindication to the placement of implants. Parafunction may be the primary, secondary, or the only cause of bone destruction as a result of forces imparted to implants by engaging, clenching, or bruxing. These forces may be intense for very short periods. The regularity and frequency of such destructive forces can have an adverse, cumulative irreversible effect on implant-supported prostheses. In a pragmatic sense, there is no way of preventing the clencher or bruxer from engaging in such parafunctional habits. Regardless, the clinician may be able to decrease the potential for destruction by adding a nightguard to the treatment protocol of implant patients.[6]

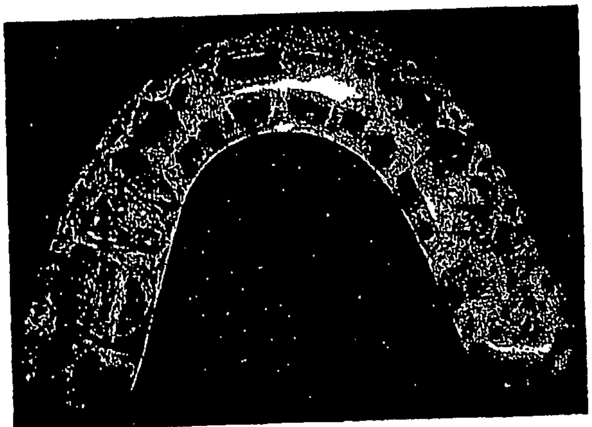

Fig. 1. The external aspect of the nightguard is hard, flat, and smooth. Note the relative evenness and distribution of the occlusal markings obtained with articulating paper.

NIGHTGUARDS

Although a nightguard will not prevent a parafunctional habit from occurring, an acrylic resin removable appliance superimposed over an implant-borne prosthesis can dissipate the forces of occlusion. The smooth flat occlusal plane of the nightguard allows for a gliding of opposing implant-supported prostheses over each other.

The author prefers a heat-processed acrylic resin nightguard of two consistencies. The outer (occlusal) surface (Fig. 1) is hard, smooth, and flat, whereas the inner (tooth) surface (Fig. 2) is soft and slightly resilient.

The softer inner core has frictional retention on natural and/or replacement teeth and a dampening effect through force imposition. The hard outer layer is relatively resistant to wear and, more importantly, allows for the disengagement of opposing teeth and the sliding of occlusal surfaces over each other.

The fabrication of a single nightguard (Fig. 3) is recommended. There is no need for a patient to wear

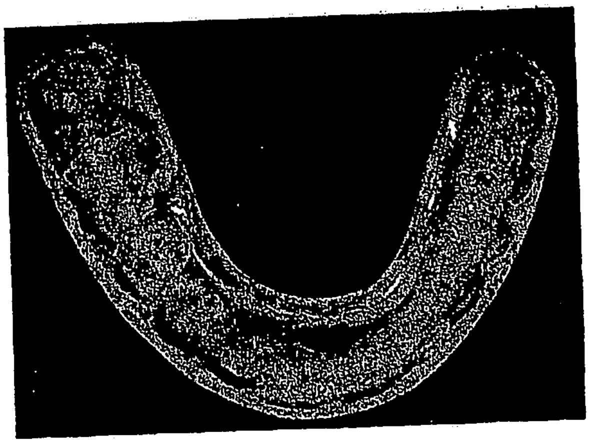

Fig. 2. The internal aspect of an acrylic resin nightguard with a soft inner portion.

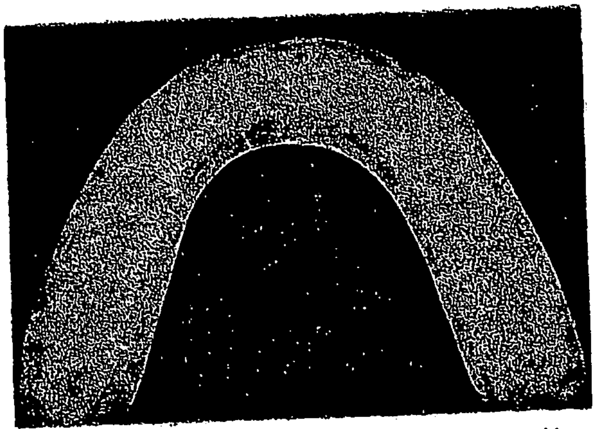

Fig. 3. The occlusal aspect of the acrylic resin nightguard has been lightly sandblasted. The chalky appearance will help the clinician to evaluate the patterns of parafunctional movements at future recall appointments.

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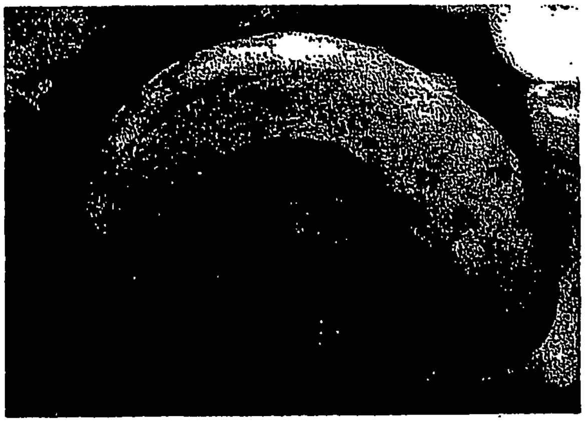

Fig. 4. An intraoral view of a nightguard in place opposing a mandibular dentition that contains a unilateral posterior implant prosthesis. Note the clarity of the occlusal markings obtained in centric closure.

both maxillary and mandibular nightguards. Encroachment on occlusal vertical dimension as a result of wearing two nightguards may cause discomfort and other problems. The arch selected for the nightguard should be the more stable of the two, have natural teeth opposing an implant prosthesis, and/or interfere least with occlusal excursions (Fig. 4).

SUMMARY

Nightguards should be considered in the treatment plans for implant prostheses patients with parafunctional habits (bruxing, clenching, or engaging). The potential exists for parafunctional habits to contribute to bone destruction, which can result in implant loss or failure.

REFERENCES

1. Brunski JB. Biomechanical factors affecting the bone-dental implant interface. A review paper. *Clin Mater.* 1992; 10:153–201.

2. Brunski JB, Skalak R. Biomechanics of osseointegration and dental prostheses. In: Naert I, van Steenberghe D, Worthington P, eds. *Osseointegration in Oral Rehabilitation: An Introductory Textbook.* Chicago, IL: Quintessence Publishing Co.; 1993:133–156.

3. Jacobs R, van Steenberghe D. Comparison between implant-supported prostheses and teeth regarding passive threshold level. *Int J Oral Maxillofac Implants.* 1993;8: 549–554.

4. Bidez MW, Misch CE. Force transfer in implant dentistry: basic concepts and principles. *J Oral Implantol.* 1992; 18:264–274.

5. Bidez MW, Misch CE. Clinical Biomechanics. In: Misch CE, ed. *Contemporary Implant Dentistry.* St. Louis, MO: Mosby-Year Book; 1993:279–311.

6. Meffert RM. Periodontitis and periimplantitis: one and the same? *Pract Periodontics Aesthet Dent.* 1993;5:79–82.

7. Academy of Denture Prosthetics. Glossary of prosthodontic terms. 5th ed. *J Prosthet Dent.* 1987;58:713–762.

8. English CE. Biomechanical concerns with fixed partial dentures involving implants. *Implant Dent.* 1993;2:221–242.

9. Monteith BD. Minimizing biomechanical overload in implant prostheses: a computerized aid to design. *J Prosthet Dent.* 1993;69:495–502.

10. Misch CE. *Contemporary Implant Dentistry.* St. Louis, MO: Mosby-Year Book; 1993:705–733.

11. Academy of Denture Prosthetics. Principles, concepts, and practices in prosthodontics–1989. 7th ed. *J Prosthet Dent.* 1989;61:88–109.

12. Yukna RA. Optimizing clinical success with implants: maintenance and care. *Compend Contin Educ Dent.* 1993;15(suppl):554–561.

13. Brunski JF. Avoid pitfalls of overloading and micromotion of intraosseous implants. *Dent Implantol Update.* 1993;4:77–81.

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